REMARKS

Applicants submit this response to the Office Action dated January 24, 2006. Claims 1-30, 43, and 44 have been withdrawn from consideration. Claim 31 has been amended to remove the dependency from withdrawn claim 1, claim 32 has been amended to depend from claim 31 instead of claim 1, and no new matter is added.

Rejections Under 35 U.S.C. § 102 (b)

Claims 31-42 were rejected under 35 U.S.C. § 102 (b) as being anticipated by Danilenko et al., SU 539878, 1976. The reference allegedly discloses a compound having antiphlogistic activity. Applicants submit that the Examiner has provided no evidence that Danilenko et al. describe a "method of antagonizing chemokine receptors." The reference is in Russian and only the translated title and one-sentence abstract were provided. Reconsideration and withdrawal of this rejection are respectfully requested.

Rejections Under 35 U.S.C. § 112

Claims 31-42 were rejected under 35 U.S.C. § 112, first paragraph, because the specification, while being enabling for some inhibiting data as given in Table 6, allegedly does not reasonably provide enablement for 1) antagonizing chemokine receptors, 2) inhibiting a chemokine mediated cellular "event," 3) inhibiting IL8, GRO-alpha driven neutrophil chemotaxis, 4) treating a disorder selected from IBD, psoriasis, ARDS, cancer, atherosclerosis, reperfusion injury, 5) inhibiting a G-protein-coupled, 7TM receptor, 6) modulating binding of peptide YY to a NPY receptor, 7) modulating the binding of a somatostatin to a somatostatin cell receptor, or 8) treating, through a therapeutically or prophalactically acceptable manner, an inflammatory "event."

Applicants submit that the specification does provide enablement for antagonizing chemokine receptors. Examples 21 and 22 provide for a number of compounds that antagonize chemokine receptors by decreasing binding of [^{125}I]Interleukin-8. Example 21 discloses a large number of compounds that have been tested with the CXCR2 receptor, and Example 22 discloses nine compounds that have been tested with five different chemokine receptors, including the CXCR2 receptor.

Applicants further submit that the specification provides enablement for inhibiting a chemokine mediated cellular "event." GRO-alpha driven neutrophil chemotaxis is an example of a chemokine-mediated cellular event. Example 21 discloses a large number of compounds that have been tested in an assay designed to measure neutrophil chemotaxis, and the data show a significant number of these that affect this process.

Applicants submit that the specification does provide enablement for treating a disorder such as IBD, psoriasis, ARDS, cancer, atherosclerosis, or reperfusion injury. A number of inflammation-related disorders have been shown to be associated with elevated levels of IL-8 and concommitant activation of CXCR1 and CXCR2 receptors. As outlined on page 3 lines 22-26, psoriasis is associated with high levels of IL-8. Similar associations are described for ARDS (page 2, lines 18-28), cancer (page 2 lines 26-27), and atherosclerosis (page 3 lines 11-16). IBD and reperfusion injury are disorders that are generally related to inflammation and likely involve similar receptor pathways. The assays described in Examples 21 and 22 demonstrate that a number of compounds have biological activity directly related to these disorders.

Applicants further submit that the specification provides enablement for inhibiting a G-protein-coupled, 7TM receptor. GRO-alpha driven chemotaxis is an example of a process that is mediated by a G-protein-coupled 7TM receptor. Example 21 provides data showing compounds that inhibit this process. Further, the chemotaxis data was obtained using cells obtained from human blood, not an *in vitro* cell culture system.

Applicants submit that the specification is enabling for modulating the binding of Peptide YY to an NPY receptor. Example 21 discloses three such compounds that inhibit binding of Peptide YY to an NPY receptor. Similarly, Example 21 discloses a compound that inhibits binding of somatostatin to a somatostatin cell receptor.

Additionally, applicants submit that the specification provides enablement for the treatment, through a therapeutically or prophalactically acceptable manner, of an inflammatory "event." The disorders described in the application may be described as inflammatory "events." The biological activities demonstrated in Examples 21 and 22 have been shown to correlate with inflammatory disorders as described on pages 2 and 3 in the specification.

Beginning on page 4 of the Office Action, the Examiner outlines the eight Wands factors to determine if the instant specification satisfies the enablement requirement. These factors are addressed below.

A specification is presumed to be enabling and the U.S. Patent and Trademark Office (PTO) has the burden of establishing a *prima facie* case of lack of enablement. See, In re Angstadt, 190 U.S.P.Q. 214, 219 (C.C.P.A. 1976); In re Marzocchi, 169 U.S.P.Q. 367, 369-370 (C.C.P.A. 1971). To make a *prima facie* case of lack of enablement, the PTO must come forward with reasons, supported by the record as a whole, showing why the specification fails to enable one of ordinary skill in the art to make and use the claimed invention. In re Angstadt, 190 U.S.P.Q. 214, 219 (C.C.P.A. 1976). The mere fact that some experimentation is necessary does not negate enablement as long as undue experimentation is not required. See M.P.E.P. § 608.01(p).

The burden is on the PTO to establish that experimentation would be undue, Angstadt, 190 U.S.P.Q. at 219, taking into consideration the eight factors that are to be considered in determining whether a disclosure requires undue experimentation. In re Wands, 8 U.S.P.Q. 2d 1400, 1404 (Fed. Cir. 1988). Applicants submit that the amount of experimentation which may be required to practice the present invention does not rise to the level of being undue experimentation, as defined by the Court in Wands.

An important aspect of the Court's decision in Wands is its finding that the nature of the technology pertinent to the Wands invention (monoclonal antibody production) permitted a broad definition of the term "experiment." The Court found that an "experiment" in the monoclonal antibody art consisted of the entire attempt to make a monoclonal antibody against a particular antigen. As described by the Court, the process entailed, "immunizing animals, fusing lymphocytes from the immunized animals with myeloma cells to make hybridomas, cloning the hybridomas, and screening the antibodies produced by the hybridomas for the desired characteristics." 8 U.S.P.Q. 2d at 1407. Thus, Wands supports the conclusion that, in a complex field such as monoclonal antibody production, the entire attempt to achieve the desired result, from beginning to end, constitutes one experiment.

According to the Court, repetition of this whole experiment more than once does not constitute undue experimentation. As the Court indicated, practitioners in the art would be prepared to screen negative hybridomas in order to find a hybridoma making the desired antibody. 8 U.S.P.Q. 2d at 1406. Thus, the fact that some aspects of the experiment as a whole will yield negative results does not mandate a finding that the amount of experimentation to achieve a positive result is undue.

Like the production of monoclonal antibodies, the identification of compounds for use in the methods as claimed may require some experimentation, but if viewed in the light of Wands, this experimentation, and the possibility of encountering negative results along the path to the positive results, is not undue. Furthermore, the present applicants provide extensive guidance to allow one of ordinary skill in the art to obtain a polypeptide that is within the scope of the claims.

Applicants submit that one of ordinary skill in the art can identify a compound as recited in claim 31 and assay it for inhibiting a chemokine-related cellular event. Such experimentation is standard in pharmaceutical research and discovery. Such assays would not constitute "undue" experimentation within the scope of Wands, as discussed in detail below. Applying this information to the eight Wands factors, one of skill in the art would conclude that undue experimentation would not be required to practice the claimed invention.

1. *Quantity of experimentation necessary.* The only experimentation required is the performance of assays as described in the specification. These procedures are routine and would not have to be done repeatedly before a definitive result was obtained. Because the inventors and the art provide means for the objective assays, this factor is met, for example, by the ability of the claimed compounds to inhibit the binding of cytokines to specific chemokine receptors. This is described in detail in the specification at pages 47-68.

The Wands Court found that practitioners in the art are prepared to screen negative hybridomas to find one that made the desired antibody. (8 U.S.P.Q. 2d at 1406) The Court further stated that an "experiment" was not simply the screening of a simple hybridoma, but instead was the entire attempt to make a monoclonal antibody against a particular antigen. This process included immunizing animals, fusing

lymphocytes from the immunized animals to make hybridomas, cloning the hybridomas, and screening the antibodies produced by the hybridomas. (8 U.S.P.Q. 2d at 1406)

By analogy, a single experiment in the present art could include testing compounds as claimed in a series of well-studied experimental protocols, as is the case with any small molecule destined for the clinic. The Examiner stated that "it is not clear who the patient in need thereof is who would require the antagonizing or inhibiting treatment . . . ." (Page 6, lines 9-10) As described in detail above at page 11, several well-known disease states are associated with activation of CXCR1 and CXCR2 receptors, particularly in association with elevated levels of IL-8. The method of the claims relies on this underlying disease mechanism. As in all pharmaceutical research, some members of the claimed class of molecules may not be effective. However, encountering negative results would not mean that undue experimentation is involved, according to Wands.

In Wands the inventors randomly took a small subset of their frozen, stored hybridomas and tested them, finding that a certain percentage of the antibodies possessed the desired binding affinity. The Court noted that there was a discrepancy about whether the percent success should be measured against the antibodies tested or the total number left in the freezer and untested. The Court found that even if the success rate was very low, that would not defeat enablement if the experimentation was not undue:

> Even if we were to accept the PTO's 2.8% success rate, we would not be required to reach a conclusion of undue experimentation. Such a determination must be made in view of the circumstances of each case and cannot be made solely by reference to a particular numerical cutoff.

(8 U.S.P.Q. 2d at 1406, fn29)

2. *Amount of direction or guidance provided.* Regarding the amount of direction provided by the inventors, the Examiner stated that "there are no examples with the R being heterocyclic groups and also there is no data provided to show that these compounds do indeed treat various diseases." However, the sixth and ninth compounds on page 51 as well as the last compound on page 58 are heterocyclic compounds that were tested in the IL-8 binding assay and the GRO-α ChTx assay.

The specification provides clear directions for performing the experimentation, and cites to published scientific articles for details not mentioned in the specification. Similarly, the Wands Court found that the starting material was available to the public (as is the material used in the present application) and the patent at issue in Wands provided a detailed description of the methods. (8 U.S.P.Q. 2d at 1404, 1405)

3. *Presence of absence of working examples.* Regarding the "existence of working examples," the Examiner states that the specification only discloses nine examples "with a few assays." However, Tables 3-6 show that 95 compounds were tested. In any event, Wands permits experimentation as long as it is not undue. One of skill can routinely test other compounds as described in the Examples.

4. *Nature of the invention.* The nature of the invention involves assays and assay interpretation that are well-known to those of ordinary skill in the art. The Court in Wands stated that the nature of monoclonal antibody technology is that it involves screening, including screening of negative samples (in that case, hybridomas). The number of potentially negative samples was not viewed as a determining factor in reaching a finding of undue experimentation. (8 U.S.P.Q. 2d at 1406-1407)

By analogy, the assays described in the specification refer to methods published in well-known journals, such as those cited on pages 64-66. Because the invention is in the pharmaceutical arts, one of skill would expect to perform further work to adapt the disclosed methods and compounds to *in vivo* use.

5. *The state of the prior art.* The Wands Court found that "all the methods needed to practice the invention were well known." (8 U.S.P.Q. 2d at 1406) Similarly, the methods of assaying the activity of compounds and interpreting the assay results are well known. These well-known assays are applied to the novel compounds for the methods claimed in claims 31 and 32. The Examiner states that "there is no absolute predictability and no established correlation between *in vitro* activity and the treatment of various diseases and also the IC50 values, as in the *in vitro* data is not a reliable predictor of success even in view of the seemingly high level of skill in the art." The Examiner also states that inhibiting cellular events or treating disease related to chemokine receptors and G protein–coupled receptors is "not an absolute predictability." (Page 4, lines 18-19) Absolute predictability is not the standard under

Wands. The Examiner cited Cummings, C.J., J. Immunol. 162:2341-2346 (1999) to support the alleged complication of selecting therapeutic targets to reduce inflammation. However, the article actually helps to simplify the process. At page 2345, the last paragraph states,

> These data simplify an otherwise complex and redundant system of CXC chemokines and receptors and focus attention on the importance of CXCR1 in sepsis. These studies suggest that a CXCR1 receptor-targeted strategy to limit inflammation in patients with sepsis will reduce PMN migration to CXC chemokines, yet preserve PMN responsiveness to bacterial products.

Furthermore, the teachings of Cummings, which was published several years before the filing date of this application, form part of the background knowledge of those of skill practicing the invention. The paper also states that the observations extend previous findings and "demonstrate their relevance to human disease." (Page 2345, lines 35-37)

6. *The relative skill of those in the art.* Those of skill in this art are highly skilled and would be competent at designing and performing, or directing the performance of, the procedures of factors (3) and (4) above. The Wands Court found that the level of skill in the monoclonal antibody art was high at the time the application was filed, but, importantly, the Court found that development of skill in performing specific experiments relevant to the art did not preclude enablement. Specifically, the Court stated that initial failures occurred as the inventors learned to fuse cells, and "[o]nce they became skilled in the art, they invariably obtained numerous hybridomas ..." that met the claim limitations, 8 U.S.P.Q. 2d at 1406. By analogy, it would not defeat enablement for one of skill in the present art to test the compounds disclosed for use in the disease states and conditions as claimed. As the Examiner notes, "the ordinary artisan is highly skilled." (Page 5, paragraph 4.)

7. *The predictability or unpredictability of the art.* Regarding the level of predictability in the art, the Examiner states that the pharmaceutical art is unpredictable, and cites In re Fisher, 427 F. 2d 833, 166 U.S.P.Q. 18 (CCPA 1970).

First, the Examiner states, "that the pharmaceutical art is unpredictable, requiring each embodiment to be individually assessed for physiological activity," at page 5 of the

Office Action, paragraph 5. Applicants respectfully request that the Examiner provide statutory or case law support for that statement.

Second, In re Fisher is not on point for the present issue. Fisher does state that the scope of enablement varies inversely with the degree of unpredictability of the factors involved. However, this was in reference to claim limitations on potency of the materials, in that case a biological preparation of ACTH (adrenocorticotrophic hormone). The claims recited a potency of "at least 1" International unit per milligram.

The Court questioned whether an inventor should dominate "future compositions having potencies far in excess of those obtainable from his teachings plus ordinary skill." (427 F.2d at 839.) The Court also noted that the recitation was "open ended" with no upper limit. This fact pattern is distinct from the present situation in which a finite, closed set of compounds is recited in claims 31 and the claims depending thereon.

In Wands, the Court noted that the cell fusion technique was well known to those of ordinary skill in the art, and that there was no indication that the fusion step should be more difficult or unreliable for the antigen in question (HBsAg) than for other antigens. The Examiner has provided no evidence that the testing of additional compounds of the invention would be "more difficult or unreliable" (8 U.S.P.Q. 2d at 1406) than for those tested according to the Examples. One of skill in this art expects to conduct extensive experimentation for the very reasons mentioned by the Examiner, such as the effect of the R groups.

8. *The breadth of the claims.* The Examiner states at page 4, paragraph 1, that the compounds cover a wide range of compounds. This is the case with pharmaceutical claims, and the presence of potentially non-operative embodiments does not defeat enablement.

The Examiner cited Genentech Inc. v. Novo Nordisk and quotes the "hunting license" analogy from Brenner v. Hanson, 148 U.S.P.Q. 689, 696 (1966). First, this language related to a utility requirement, and so its sweeping second-hand application to an enablement issue is inappropriate. Furthermore, citing a utility-related quote from Brenner ignores the fact that the underlying situation in Genentech fails to support lack of enablement of the present claims. As the Genentech Court states,

> Novo further argues that neither the specification nor the

> references cited by Genentech suggest a single amino acid sequence, out of the virtually infinite range of possibilities. 42 U.S.P.Q. at 1004.
>
> [W]hen there is no disclosure of any specific starting material or any of the conditions under which a process can be carried out, undue experimentation is required. 42 U.S.P.Q. 2d at 1005. (Emphasis added.)

The present specification and claims do not fall into this category, and Genentech Inc. v. Novo Nordisk fails to support the alleged lack of enablement.

In view of the foregoing remarks, applicants submit that the Examiner has not met her burden of making a *prima facie* showing that undue experimentation is required in order to practice the invention as claimed. Reconsideration and withdrawal of this rejection are respectfully requested.

Commissioner is hereby authorized to charge the required fees to Deposit Account No. 04-0258. If additional fees are believed necessary, the Commissioner is further authorized to charge any deficiency or credit any overpayment to Deposit Account No. 04-0258.

All of the claims remaining in the application are now believed to be allowable. Favorable consideration and a Notice of Allowance are earnestly solicited.

If questions remain regarding this application, the Examiner is invited to contact the undersigned at (206) 628-7650.

Respectfully submitted,
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